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Statement of Purpose:
AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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Resume requested by March 21, 2003.

Warning, Counterfeit Procrit® (Epoetin Alfa).....

The FDA and Ortho Biotech have warned health professionals and patients to check for counterfeit Procrit, which may contain dangerous bacteria and have no active ingredient.

Retroviruses Conference Clinical News: Interview with Cal Cohen, M.D.

by John S. James

Cal Cohen, M.D., has been an AIDS physician since the mid 1980s. Currently he is research director of the Community Research Initiative of New England, and teaches at Harvard Medical School in Boston, Massachusetts. He has a clinical practice in Boston at Harvard Vanguard Associates.

We asked Dr. Cohen to discuss some of the most important information from the 10th Conference on Retroviruses and Opportunistic Infections, February 10-14 in Boston -- focusing mostly on the news that physicians and patients can use now.

This is part 1 of the 2-part interview.

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Dr. Cohen: Some of the clinical highlights of this conference were:

* More proven options for beginning antiretroviral therapy;

* More information on switching antiretrovirals if necessary -- including possible options on delaying the switch until a better new regimen is available,

and also information on structured treatment interruption;

* Reports on lipodystrophy, heart-disease risk, and other side effects of some antiretrovirals;

* Viral resistance to drugs, and ways to minimize it; and

* New drugs in the pipeline -- a "bumper crop," as one prominent researcher said.

Starting Antiretroviral Therapy

Dr. Cohen: At this meeting we saw more data about the differences in the second year of taking d4T (Zerit®) vs. tenofovir (Viread®).[1] About 600 volunteers were randomly assigned to take one or the other of these drugs; in either case they also took 3TC (Epivir®) and efavirenz (Sustiva®). The trade-off presented was good news for tenofovir on safety; only 1% of the patients had lipodystrophy (as defined by the researchers) vs. 12% for d4T. Tenofovir patients had less neuropathy as well (not a surprise) -- and also a better lipid profile. The safety certainly favors tenofovir. Yet many patients can tolerate d4T; in this trial more than 80% of those on d4T did not have visually apparent lipodystrophy even after two years.

Is there some way to predict who is most vulnerable to lipodystrophy? Researchers are working on that. And if lipodystrophy does develop, how reversible is it? We have learned at this and other meetings that it can be reversible, especially if we catch it early enough.

The tradeoff on tenofovir plus 3TC (vs. d4T with 3TC) is what may happen with resistance. If someone does develop virologic escape from this tenofovir starting regimen, about 25% of the time they will have the K65R mutation (but that was only about 1% of the patients in this trial -- see below). This mutation, along with the 3TC resistance mutation M184V, can create resistance to many of the other nucleosides, and leave only AZT and d4T predicted to be active nucleoside drugs for people with these mutations.

But with d4T plus 3TC, if you get resistance and viral rebound, usually you only get resistance to the 3TC and less likely to d4T, which has a different genetic barrier to viral resistance. In the tenofovir vs. d4T trial above, of the 28 people who had virologic escape, there were 2 cases of K65R on d4T and 7 with tenofovir. So the difference is all of 5 people, in a study of 600 -- a difference of about 1% so far, having the additional risk of getting the more serious viral resistance with the tenofovir. Still this is the trade-off people need to consider -- increased risk of lipodystrophy, vs. the extra 1% risk of worse cross-resistance to nucleoside analogs.

One possible way to minimize both lipodystrophy and cross resistance is for somebody to start on d4T for perhaps six months, then switch over to tenofovir once their viral load is clearly less than 50 copies, for example. Most important with either regimen, however, is to make sure that the treatment is working and suppressing the virus.

James: Even though d4T may work well for some patients, is it still agreed that nobody should use d4T plus ddI, because of the toxicity of the combination?

Dr. Cohen: Yes. While both drugs have uses separately in some patients, they should not be used in combination.

Efavirenz vs. Nevirapine in Starting Regimens

Dr. Cohen: The so-called 2NN study (for 2 non-nucleosides) had four arms. It

compared efavirenz (Sustiva® in the U.S., also known as Stocrin® in some countries), vs. nevirapine (Viramune®) once a day, vs. nevirapine twice a day, vs. the combination of efavirenz and nevirapine. All volunteers also received d4T plus 3TC. This study enrolled over 1200 volunteers in 17 countries in Europe, North and South American, Australia, and South Africa.[2,3]

The first, easy conclusion is that there is no good reason to combine nevirapine and efavirenz; that arm did not do better in any important way, so we can forget that combination. In comparing nevirapine once vs. twice a day, there was a demonstration of more liver toxicity in the once a day arm vs. twice a day. So it may be safer to consider nevirapine a twice a day drug, even though in overall success they seemed about equal.

What about comparing efavirenz vs. nevirapine, one main purpose of this study? They were more similar than different but technically not equivalent. Some prior studies have not done well for nevirapine. This one, the first head-to-head comparison with efavirenz, increased the data supporting nevirapine as a decent drug.

The problem is the toxicity profile of nevirapine, including a higher percent of liver toxicity with either once or twice a day nevirapine than with efavirenz. Two deaths among the 800 or so volunteers taking nevirapine in this study were attributed to nevirapine [one from liver failure, the other from an antibiotic-resistant staph infection acquired in a hospital while recovering from Stevens-Johnson syndrome]. We have known from other studies that there is a rare but potentially fatal liver complication that occurs in the first weeks or months of use of nevirapine. This was reported for example in the study of FTC vs. 3TC done a few years ago in South Africa -- where reports of very rare but fatal liver toxicity were noted. This is another factor to consider as we construct the first regimen for a patient.

James: Do we know from that study if the person who died of liver failure was monitored correctly for liver toxicity?

Dr. Cohen: We do not know yet from the report at this conference, and it would be helpful to learn from the company if this occurred despite monitoring, or if this volunteer was not monitored according to the protocol. It is important to know if the recommended blood tests could usually find this liver problem in time.

So on nevirapine this trial provides more data to inform the choice. It does not tell us which drug is better.

It is still fair to say that Sustiva (efavirenz) is at least as good as Viramune (nevirapine), and may be better in some ways. There was nothing presented that made nevirapine a better choice -- except for those who cannot tolerate the well-known efavirenz side effects of vivid dreams and mood changes. Overall, nevirapine is probably just as good or slightly worse on average. The statistics for this trial allow us to state with confidence that nevirapine is similar and no more than 12% less successful than efavirenz.

Protease Inhibitor Information

Dr. Cohen: Within the protease inhibitors, we saw new data from the drug 908, which is the reformulation of amprenavir. It did much better than nelfinavir, and impressively it did well even at much higher viral loads. It may be the best data we have seen in an un-boosted protease inhibitor doing well at high viral loads.[4,5,6]

It is not clear if clinicians will choose to use 908 earlier in treatment (when this drug is approved), because there are

some lipid disturbances. But 908 certainly is interesting in the same way that Kaletra is interesting, because not only is it very potent, but also if you do get viral escape and rebound, boosted protease inhibitors including 908 plus low-dose ritonavir did help protect from resistance not only to the protease inhibitors, but also to the other drugs in the regimen.

[Note: a "boosted" protease inhibitor means that the drug is used in combination with another protease inhibitor -- often but not necessarily a small dose of ritonavir, which slows the body's metabolism of many drugs, thereby keeping the blood level of the other protease inhibitor high. Kaletra (lopinavir plus ritonavir) is automatically boosted, because it includes a small ritonavir dose in the pill.]

One of the most attractive things about a boosted protease inhibitor as a starting regimen is not only its potency, which is clear and established, but also this high genetic barrier to resistance. For some patients -- particularly those whose adherence may be spotty or erratic -- the danger of using a non-nuke (efavirenz or nevirapine) is that the patient might lose it early in their treatment to viral resistance, due to poor adherence. If someone might not be ready to start antiretroviral therapy but wants to give it a try, there is something to be said for the boosted protease inhibitor and taking advantage of that high genetic barrier to resistance. (Of course, if someone has side effects from ritonavir, for example gastrointestinal upset, then the regimen becomes less desirable as a way to find out if one wants to be on treatment. Therefore many physicians prefer to start with two nucleoside analogs and a non-nuke for beginning treatment -- another tradeoff to consider.)

Data on 908 had been presented earlier at the Glasgow meeting. At the Retroviruses meeting, a poster provided data about the lack of viral resistance on boosted 908.[6] The researchers did not find protease inhibitor resistance in that arm -- and indeed, found less resistance to the nucleosides as well. It probably takes more non-adherence to get viral rebound on a boosted protease inhibitor than on the other available antiretroviral regimens. If you do rebound it is probably because you stopped the drugs, not because you missed a few doses.

A new experimental protease inhibitor -- atazanavir -- looks attractive because of its lack of lipid disturbances. This drug does not have a lot of the toxicities including insulin resistance that have tainted protease inhibitors so far.[7]

The other piece of the puzzle on atazanavir can be seen as an evolution of three stages of controversy around resistance and cross-resistance.

The first-generation discussion was the nelfinavir vs. indinavir battle, in which nelfinavir had a more salvageable pathway (meaning better treatment options if resistance does develop to the drug).

The second battle was the boosted PI, where no resistance developed when those drugs were used.

And now we have a third version of the story, which is if you use atazanavir first and get rebound, you actually get hypersusceptibility of the virus to other protease inhibitors -- meaning that the virus is more susceptible to the drugs (at least predicted, based on the mutations seen). The clinical meaning of that is not yet known. But we do have information about hypersusceptibility with other drugs, suggesting that it does seem sometimes to make a difference. So it may or may not sway clinicians to want to use it for that reason. And there are controversies around whether atazanavir is as potent a drug as we might need for

some patients. There may be some patients with a high viral load and low CD4 where you may not want to trust atazanavir, at least with two nukes. It does add another layer of controversy or complexity in what makes these regimens attractive.

Overall, it was a very good meeting in making us feel that we have more options than before, more attractive options, and different ways to balance the tradeoffs. So we feel less stuck, with more flexibility.

Antiviral Drug Toxicity

Dr. Cohen: This meeting also focused on blood cholesterol and lipids, with analysis of data from a very large cohort of study volunteers in Western Europe and the U.S., to see if there is any evidence of increased risk of heart disease in those on treatment. As you know, this analysis, called the D.A.D. study, did find an increase of about 25% in the rate of heart attacks [per year of exposure] in people on any antiretroviral treatment.[8]

The limitation of this study, or at least the analysis done so far, is that it did not sort out which drugs may be more likely or less likely to cause heart disease. Given that HIV treatment is needed, this study said there is a risk but did not say what to do about it. It did not entirely answer whether the lipid effect of treatment completely explains the problems -- meaning that if you avoid the lipid problem then can you avoid the risk (the alternative is that there is some other mechanism at work). One of the surprising and confusing points of the analysis presented is that they found that those who had lipodystrophy had a *lower* risk of heart attacks. In general, drugs that cause lipodystrophy tend to have more blood cholesterol and triglyceride problems. So you have the paradox, in that one effect of these drugs is to increase lipids, and the other effect is to increase lipodystrophy, but these seem to go in opposite directions on heart risk. So while there is cause for concern, this trial does not yet tell us what to do -- other than avoid smoking, since nothing has changed about that.

Choosing different drugs is still a question of trade-offs; there is still no perfect regimen, although we get closer. At this meeting, the news on the nucleosides was the differences between them -- and particularly, since almost everybody continues to agree that 3TC is such a good drug that it deserves to be used up front, the question of which nucleoside you pair with it.

Note: Part 2 of this 2-part interview will include treatment interruption, "deep salvage" in very treatment-experienced patients, an experimental human monoclonal antibody, and a brief summary of some of the major take-home messages for doctors and patients.

References

Unless otherwise stated the references are to the 10th Conference on Retroviruses and Opportunistic Infections, Boston February 10-14, 2003.

Note: You can find all of the following abstracts at the official conference site, http://www.retroconference.org; they will remain there for about a year. To find a particular abstract, you can either search for the poster number, for an author, or for a word in the title. You can also search by subject -- by looking for all abstracts that contain a particular key word, such as the generic name of a drug. In the listing below we indicated if a poster is also available online with the abstract (as of March 1, 2003, when we checked -- other posters may be added later). Researchers were encouraged but not required to submit online posters (for oral as well as poster presentations), which have more information than the abstracts. Usually these posters were submitted digitally, not as photographs, so they can be seen and read clearly online.

The abstracts and posters should be readable on all computers, but you need (1) to have the free Acrobat reader for the posters (if you do not already have it, you can download it from http://www.adobe.com/products/acrobat/readstep2.html), and (2) to *not* have your browser's Internet security setting too high, or the software to search

the abstracts may not work. (Unfortunately the Webcast sessions, also on the official site, use a Microsoft format and can only be heard on Windows.)

1. S Staszewski, JE Gallant, AL Pozniak, and others. Efficacy and safety of tenofovir DF (TDF) versus stavudine (d4T) when used in combination with lamivudine and efavirenz in antiretroviral naïve patients: 96-week preliminary interim results. [Abstract #564b]

2. F van Leth, E Hassink, P Phanuphak, and others. Results of the 2NN study: a randomized comparative trial of first-line antiretroviral therapy with regimens containing either nevirapine alone, efavirenz alone or both drugs combined, together with stavudine and lamivudine. [Abstract #176]

3. F van Leth, P Phanuphak, B Gazzard, and others. Lipid changes in a randomized comparative trial of first-line antiretroviral therapy with regimens containing either nevirapine alone, efavirenz alone or both drugs combined, together with stavudine and lamivudine (2NN Study). [Abstract #752 - Poster available]

4. J Nadler, A Rodriguez-French, J Millard, and P Wannamaker. The NEAT Study: GW433908 efficacy and safety in ART-naïve subjects, final 48-week analysis. [Abstract #177]

5. E DeJesus, A LaMarca, M Sension, C Beltran, and P Yeni. The Context study: efficacy and safety of GW433908/RTV in PI-experienced subjects with virological failure (24 week results) [Abstract #178]

6. S Macmanus, P Yates, S White, N Richards, and W Snowden. GW433908 in ART-naive subjects: absence of resistance at 48 weeks with boosted regimen and APV-like resistance profile with unboosted regimen. [Abstract #598 - Poster available]

7. R Murphy, V Pokrovsky, W Rozenbaum, and others. Long-term efficacy and safety of atazanavir with stavudine and lamivudine in patients previously treated with nelfinavir or ATV: 108-week results of BMS study 008/044. [Abstract #555 - Poster available]

8. N Friis-Moler, R Weber, A D'Arminio Monforte and others. Exposure to HAART is associated with an increased risk of myocardial infarction: The D:A:D Study. [Abstract #130]

First AIDS Vaccine Tested Did Not Protect, But Gives Scientific Leads

by John S. James

The first "phase III" trial -- one large enough to determine whether a treatment works -- of an AIDS vaccine in humans found that the vaccine (called AIDSVAX, produced by VaxGen in Brisbane, California) failed to protect people from HIV infection. But thousands of blood tests now being analyzed will likely provide important information for making better vaccines. Some of this work will be reported at the "HIV Vaccine Development: Immunological and Biological Challenges" meeting beginning March 29 in Banff, Canada.

Many scientists did not expect AIDSVAX to work, because this vaccine only produces antibodies against HIV and does not stimulate another branch of the immune system called cellular immunity. Recently, however, there has been renewed interest in antibodies -- partly because of growing knowledge about how to select the right antibodies, and also because cellular immunity alone may not prevent infection but only slow disease development. HIV vaccines might need to use both.

The VaxGen report led to controversy because of suggestions that AIDSVAX might work partially in Blacks, or Asians. In Black volunteers, only 4 of 203 who received the vaccine later became infected with HIV, compared to 9 of 111 who received the placebo; in Asians the numbers were 2 of 20 vs. 2 of 53. There is a widespread consensus that no conclusions about human effectiveness can be drawn from such small numbers -- although more research is needed to look for possible racial differences, and this work has started. (This vaccine is not relevant to Africa because it was made specifically for the clade B virus, which causes the AIDS epidemic in the U.S., Europe, and some other areas, but is not common in Africa, where AIDS is caused by clade C and other clades of HIV.)

For more information on the science

and controversy around the February 24 VaxGen report, see:

* "Understanding the Results of the AIDSVAX Trial, by AVAC, the AIDS Vaccine Advocacy Coalition, http://www.avac.org/, or directly at: http://www.avac.org/pdf/UnderstandingAIDSVAX.pdf (capitalization *does* matter).

* Articles by Jon Cohen in *Science* magazine, February 28, 2003 and March 7, 2003 (and any following issues).

T-20: Most Expensive AIDS Drug Ever at $25,000 Per Year?

by John S. James

On February 24 Hoffmann-La Roche Ltd. announced a European price for T-20 [Fuzeon®], an experimental drug expected to be approved soon by the U.S. FDA, probably in March 2003 [Note: it was approved March 13]. The price, 52 Euros per day or almost $21,000 per year, is expected to be close to the U.S. price, which will not be announced until the drug is approved. If so, U.S. retail prices are likely to be around $25,000 per year, several times the cost of other AIDS drugs.

Roche said that the price "reflects the structural complexity of Fuzeon and its highly sophisticated manufacturing process" requiring more than 100 production steps. Trimeris, Inc. and Hoffmann-La Roche Inc. (the U.S. branch of the Swiss company) said that "U.S. patients currently enrolled in the FUZEON Early Access Program will continue receiving FUZEON for free until it is commercially available and participants' reimbursement can be achieved." (Trimeris, Inc. is the small company that initially developed T-20. It was then was acquired by Roche, which financed the improved manufacturing, large clinical trials, and other work needed for commercialization.)

The AIDS Treatment Activist Coalition (http://www.atac-usa.org) said, "It is a tragic state of affairs in drug development when an encouraging breakthrough drug cannot be accessed by the people who need it most."

Comment

T-20 (also called FUZEON™, or enfuvirtide) is not a miracle drug. It is about equally effective as other AIDS drugs, and considerably more difficult to use, because it must be carefully mixed by the patient, and injected twice per day. The advantage is that T-20 is in a different class of drugs and works entirely differently than other approved HIV treatments, so virus that has become resistant to the other drugs is still susceptible to T-20. Patients whose virus has become resistant need two or more highly active antiretrovirals as a basis for a combination that may get the virus under control again, and T-20 could be one of those. But only a minority of patients would use T-20 even if price were not an issue.

It is true that T-20 is difficult to manufacture and has been expensive to develop. But how can the company get its investment back if the price is so high that few of those who need the drug (already a small market) can obtain it? Private insurance has years of experience in getting rid of persons with HIV and other expensive patients, who then end up in public programs. These programs, like Medicaid and ADAP, are facing unprecedented financial pressures and